This Month in the *Journal*

The *Journal* is sorry to report that Dr. Norman Spencer (a.k.a. Harrison Ford) will not be presenting his work on DNA repair at the ASHG meeting this year. We would still like to thank him for accurately portraying the glamorous life of a geneticist in the movie *What Lies Beneath*. We at the editorial office screened the movie in the hopes of catching a glimpse of the *Journal,* since the movie studio asked permission to use it on the set. Although positive identification was difficult because of glare off the *Journal*'s cover, we think that it was sitting next to another genetics journal, which will remain nameless. Despite our fleeting big-screen debut, the movie got four thumbs up and two screams from us.

This month in the *Journal,* Frederick Moore and Renee Reijo-Pera (p. 543), present an editorial on mtDNA and male sperm motility. They discuss the findings, by Ruiz-Pesini et al. (p. 682), that mtDNA haplogroup T is associated with low sperm motility and that this may be due to slight decreases in the activity of the oxidative phosphorylation system in this haplogroup. In addition to providing new information about untreatable male subfertility, this work implicates mtDNA variation in the phenotypic modulation of other disorders.

Iron-Frataxin Multimers, *by Adamec et al.* **(***p. 549***)**

Blame it on free radicals again! Evidence of oxidative damage, as well as iron-storage problems, are evident in patients with Friedrich ataxia (FRDA), but the explanation for this damage has not been understood. Defects in the mitochondrial protein frataxin are the primary cause of FRDA, an autosomal recessive neuro- and cardio-degenerative disease, but the relationship between frataxin and oxidative damage has been unclear. Grazia Isaya and colleagues have done extensive experimentation to demonstrate that frataxin is involved in iron sequestration. They find that frataxin complexes into 60-mers in an iron-dependent fashion. Although frataxin monomer cannot bind iron, the multimer can sequester an estimated 3,000 iron atoms in a bioavailable form. The multimers are not simply nonspecific frataxin aggregates, because (1) the multimerization is specifically induced by iron, (2) it occurs in an ordered process, and (3) the multimers can be fractionated, in complex with iron, from yeast. Adamec et al. propose that this iron-sequestration function is important for iron bioavailability in mitochondria and that loss of this function in patients with FRDA leaves them susceptible to iron-induced oxidative damage.

Turner Syndrome Neurocognitive Phenotype, *by Ross et al.* **(***p. 672***)***; and* **VCX *in X-Linked Mental Retardation,*** *by Fukami et al.* **(***p. 563***)**

Rather than a nonspecific mental retardation, the cognitive defects associated with Turner syndrome are limited to motor function, visual-spatial abilities, nonverbal memory, visual-perceptual abilities, and attention. Although there are likely to be hormonal and environmental influences on this phenotype, some of the defects are likely to result from direct genetic effects. Judith Ross and colleagues (p. 672) have studied patients with partial monosomy for Xp and have identified a genetic region that is associated with the Turner syndrome neurocognitive phenotype. This region maps to distal Xp22.3 and falls within the pseudoautosomal region PAR1. Also mapping to Xp22.3 is the *VCX-A* gene, which is deleted in males with X-linked nonspecific mental retardation. This gene was identified by Fukami et al. (p. 563), who employed a procedure similar to that used by Ross et al. Could the cognitive defects in Turner syndrome be genetically linked to those in X-linked nonspecific mental retardation? The critical regions identified in the two studies do not directly overlap. However, larger deletions in the Xp region can be associated with both disorders, and it is tempting to speculate that some genes play a modulating role in the cognitive deficits of both disorders.

Genetic Polymorphisms and Down Syndrome Risk, *by Hobbs et al.* **(***p. 623***)**

Folate metabolism is intimately involved in DNA synthesis and the proper methylation of DNA. Methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) catalyze reactions in the biochemical pathway that generates the major methyl donor for DNA, RNA, protein, and phospholipid methylation. Folate deficiency is associated with several DNA defects, including DNA strand breaks, altered recombination, abnormal DNA methylation, and chromosome missegregation. This has led Jill James and colleagues to study the relationship between MTHFR, MTRR, and Down syndrome. They have wondered whether defective folate metabolism would lead to increased nondisjunction and, therefore, to Down syndrome. In this issue, they present a study in which they calculated the maternal risk of Down syndrome in association with poly-

0002-9297/2000/6703-0001$02.00

morphisms in the genes for MTHFR and MTRR. They found that both the 677CT polymorphism in MTHFR, which reduces the enzyme's activity, and the 66AG polymorphism in MTRR increase the risk of having a child with Down syndrome. In combination, the polymorphisms had an additive effect, giving a 4.08-fold-increased risk of Down syndrome. It is also possible that a folate deficiency may exacerbate the effect of these polymorphisms and may increase this risk even further. The association of maternal MTHFR and MTRR variation with Down syndrome provides a possible link between intermediary metabolism and nondisjunction.

Ancestry of Icelandic Y Chromosomes, *by Helgason et al.* **(***p. 697***)**

In the March 2000 issue of *AJHG* (66:999–1016), Agnar Helgason and colleagues examined mtDNA lineages from modern Icelanders and found that the majority of founding females for the Icelandic population came from the British Isles. In a supplemental study, they examined the Y-chromosomal lineage for the same population, and they report the results in this issue (p. 697). Through an analysis of diallelic and microsatellite variation in Icelanders, they have developed a phylogenetic network for the Y chromosomes of this population. Comparison of the Icelandic Y-chromosome variation with that of modern Scandinavian and Gaelic populations has identified a closer relationship between the Icelandic and Scandinavian chromosomal pools than between the Icelandic and Gaelic pools. These results suggest that the male founder lineages for the Icelandic population were largely Scandinavian; this is in contrast to the female founders, who were largely Gaelic. Together, these studies correlate with historical evidence that suggests that male Norse invaders of the British Isles eventually intermarried with the resident females and that some of these family groups went on to settle Iceland.

Report (PPH1 *Is BMPR2*), *by Deng et al.* **(***p. 737***)**

This month in the *Journal,* Deng et al. show that patients with familial primary pulmonary hypertension (PPH) have mutations in the bone morphogenetic protein receptor II (BMPR2) gene. PPH is a very serious, progressive condition characterized by lesions that cause constriction of the pulmonary arterial blood vessels. The resulting hypertension leads to heart failure and death, generally within 3 years of diagnosis. Sporadic cases of this disorder are more common and can be caused by the appetite-suppressant drugs phentermine and fenfluramine, which, in combination, are known as "phen-fen." Because of these effects, phen-fen is no longer available in combination. BMPR2 is a cell-signaling protein that plays a role in lung development, and the mutations in this gene are believed to reduce signaling in the BMP pathway. This, in turn, could lead to the overproliferation of cells, in pulmonary arterioles, that causes the symptoms of PPH. Delineation of this signaling pathway will lead to a better understanding of the disease process of familial PPH, and it will also help doctors to better identify those at risk for developing the disorder.

KATHRYN BEAUREGARD
Editorial Fellow